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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/817,165	04/02/2004	Arthur M. Krieg	C1039.70048US02	1597

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EXAMINER	
MINNIFIELD, NITA M	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 10/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/817,165	KRIEG ET AL.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 19 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 19 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 02 April 2004 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892) 4 pgs.
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' preliminary amendment filed April 2, 2004 is acknowledged and has been entered. Claims 1-18 have been canceled. New claim 19 has been added. Claim 19 is pending in the instant application.

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claim 19 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-11 and 13-30 of copending Application No. 09/818918. Although the conflicting claims

are not identical, they are not patentably distinct from each other because they both claim and disclose methods of treating dermatitis or allergic reactions comprising administering to the subject a composition comprising an immunostimulatory oligonucleotide or immunostimulatory oligonucleotide and allergen.

It is also noted that Applicants have filed numerous related applications and that there could potentially be other double patenting rejections. Applicants are encouraged to apprise the Examiner of all applications that claim the same or similar subject.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

4. Claim 19 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating asthma (murine model) comprising administering to a subject during antigen specific immunotherapy a composition comprising CpG, SEQ ID NO: 10 and antigen (administering a first and second composition), does not reasonably provide enablement for the ability to treat allergy related diseases (i.e. atopic dermatitis, allergic dermatitis) or treating an allergic response to any antigen comprising administering to a subject during antigen specific immunotherapy any immunostimulatory oligonucleotide CpG, of any size and an antigen (administering a first and second composition). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The claims are directed to a method of treating an allergic response or allergy related disorder (i.e. atopic dermatitis, allergic dermatitis, etc) comprising

administering to a subject during antigen specific immunotherapy a composition comprising a CpG oligonucleotide and antigen (i.e. allergen), as well as administering a first and second composition (CpG and antigen). The CpG oligonucleotide can be of any size or formula; the only requirement is that it contain 5'CpG3'.

The specification discloses Example 12 (see p. 51), prevention of the development of an inflammatory cellular infiltrate and eosinophilia in a murine model of asthma. Mice were immunized with *Schistosoma mansoni* eggs (SEA) by i.p. injection on days 0 and 7. SEQ ID NO: 10 was administered to the immunized mice and soluble SEA was administered by intranasal instillation on days 14 and 21. After challenge the mice were sacrificed and cytokine levels and other assays conducted on the lavage fluids. The specification indicates that Figures 9-15 show that CpG/SEA induced inflammatory cells, eosinophils, to be present and generated macrophages; higher IL-12 was induced, IL-4 was reduced and IFN-gamma production increased. Applicants assert that the CpG redirected the cytokine response of the lung to production of IFN-gamma, indicating a Th1 type immune response (p. 52).

The specification does not teach that any of the other myriad of possibilities of CpG of any size or formula can be used to treat any allergic response or allergy related disorder (i.e. allergic asthma, rhinitis, conjunctivitis, eczema, atopic dermatitis) in a subject. The results shown for asthma do not indicate that the CpG will function in the same manner to treat atopic dermatitis or allergic dermatitis or any allergy related disorder.

The state of the art is unpredictable with regard to treatments using CpG. The state of the art is unpredictable with regard to allergic diseases, allergic asthma

or asthma treatments using immunostimulatory nucleic acids (i.e. CpG). CpG containing oligonucleotides are currently being investigated for exerting their immunotherapeutic effects in various organisms. Biological responses to the administration of CpG containing oligonucleotides vary, however, depending on the mode of administration and the organism (see McCluskie et al Molecular Med., 1999, 5/5:287-300 in its entirety, and especially on p. 296; see Krieg et al, Immunology Today, 2000, 21/10:521-526, especially p. 524). Wohlleben et al 2001 (TRENDS in Immunology, 2001, 22/11:618-626) studied the effects of CpG on atopic disorders such as allergic asthma. CpG-ODNs have multiple stimulatory effects on lymphocytes, including DCs, macrophages, B cells, natural killer (NK) cells and T cells (p. 619). The state of the art questions whether "CpG-ODNs can be used in humans to inhibit the development of asthma? In vitro experiments have shown clearly that human cells react to CpG-DNA in a similar manner to lymphocytes from rodents.... The results obtained from animal models suggest that it is probable that these approaches might also be successful in humans to reduce the development of atopic disorders. However, treatments using CpG-ODNs rely both on innate and adaptive pro-inflammatory Th1 immune responses to inhibit Th2 responses. For this reason, harmful side effects of the treatment need to be ruled out. Besides potential problem of inducing strong inflammatory responses at the site of exposure to allergen, the use of CpG-DNA could also have other serious side effects. It has been reported that the application of CpG-ODNs can cause septic shock in mice. A further potential problem might be the development of autoimmune disease after application of CpG-DNA. Residual autoreactive T cells might become sufficiently activated to cause disease after encountering APCs that have been unspecifically activated by CpG-DNA." (p. 620, col. 2) Wohlleben et al

teaches that all approaches that induce Th1 responses have the potential side effects of Th1-cell-mediated inflammation, potentially causing serious tissue damage (p. 624, col. 1). Kline et al 2002 (Am. J. Physiol. Lung Cell Mol. Physiol., 2002, 283:L170-L179; Kline et al, J. Immunol., 1998, 160:2555-2559) teaches that a single treatment of CpG-ODN alone was ineffective in reducing the manifestations consistent with asthma in this animal model (p. L172, col. 2; see also p. L178, paragraph bridging cols. 1-2). Kline et al 2002 teaches that splenocytes from OVA-treated mice did not develop an antigen-specific Th1 phenotype. However, mice treated with CpG ODN and OVA had a marked shift toward a Th1 response to antigen as well as reduction in airway eosinophilia, serum IgE and bronchial hyperreactivity (p. L176, col. 2).

Weiner (J. Leukocytes Biology, 2000, 68:456-463) states furthermore that the molecular mechanisms of CpG oligonucleotides' immunostimulatory effects are not yet understood (see p. 461). And while the biological effects of some chemical modifications have been studied for CpG containing oligonucleotides, such as 2'-O-methyl modifications, phosphorothioate internucleotide linkages and 5-methyl cytosine substitutions, the incorporation and positioning of chemical modifications relative to the CpG dinucleotide are highly unpredictable (see Agrawal et al Molecular Med. Today, 2000, 6:72-81, especially on pp. 78-80; pages 31-32 of the instant specification).

Hussain et al 2004 also teaches that the "[C]ombined data from our studies with the murine model of allergic rhinitis and limited data from skin favor the idea that CpG ODN may be an attractive therapy in the treatment of acute atopic dermatitis. On the other hand, chronic AD skin has significantly fewer IL-4 and IL-13 mRNA-expressing cells but higher numbers of IL-5, GM-CSF, IL-12, and

IFN-γ mRNA expression than has acute AD skin (Leung, 1999). For that reason, the long-term benefits of treatment with CpG ODN remain speculative." (see p. 27, col. 1).

Further, Satoh et al (Fukushima Igaku Zasshi, 2002, 52/3:237-250, abstract only) teaches that CpG-ODN is responsible for worsening of allergic contact dermatitis. "S.c. applied CpG ODN one day before sensitization of naïve mice significantly enhanced the ACD to DNFB which showed severe edema with massive CD8+ T cell infiltration." (abstract) Satoh et al also teaches that "[T]hese results indicate that CpG ODN vaccinations may elicit and aggravate side effects such as harmful CD8+ T cell-mediated type IV hypersensitivity responses." (abstract) Dziadzio et al (Handbook of Experimental Pharmacology, 2004, 161(Pharmacology and Therapeutics of Asthma and COPD):273-285, abstract only) teaches that "[V]arious combinations of plasmid DNA, immunostimulatory oligonucleotide (ISS-ODN), and proteins have been studied in murine models to evaluate the effectiveness of DNA vaccination. The success in skewing the immune response towards a Th1 phenotype in mice still needs to be evaluated in humans. The use of DNA vaccination as a treatment for allergic disease remains a viable option for the future." (abstract) Metzger et al (J. Allergy Clin. Immunol., 1999, 104/2 Pt. 1:260-266) teaches that oligonucleotide therapy for asthma seems unlimited, but confirmation awaits the extension from animal models to human studies (abstract only).

Further, Van Uden et al (J. Allergy Clin. Immunol., 1999, 104:902-910) teaches that although "ISS are generally considered by researchers in this field to be modular 6-mer units, it has been difficult to determine the minimum stimulatory motif length. One study showed that a minimum length of 18 bases was required

but that a length of 22 bases gave greater activity. Another study demonstrated good activity with a 15-mer ODN. Still another study used cationic lipid transfection to show a stimulatory effect with a 6-mer ODN." (p. 904, col. 1) Van Uden et al teaches that each ISS appears to have a different minimum length because crucial flanking bases would be variably distant from the core (p. 904, col. 2). Van Uden et al indicates that the ISS *may be a promising* method of treatment/prophylaxis for allergic disease, but that there are also come potential side effects that must be considered. The "immune system is delicately balanced between immunity and tolerance, between Thl and Th2, and between inflammation and unresponsiveness. There is always the possibility of unwanted effects of the powerful immune stimulation that ISS delivers." (p. 907, col. 2) LPS is similar to ISS, in view of this some of the same problems observed with LPS are potential problems with ISS (p. 907, col. 2). ISS could cause excessive local inflammation as seen with other powerful Thl adjuvants, such as CFA (p. 908, col. 1). The state of the art, taken as a whole, is still unpredictable with regard to the use of ISS-ODN in treating allergic asthma/asthma in an asthmatic subject (human or otherwise) in need of such treatment. Kussebi et al (Curr. Med. Chem.—Anti-Inflammatory & Anti-Allergy Agents, 2003, 2 :297-308) teaches that, "[I]n general, the direct conjugation of CpG-ODNs to allergenic proteins or peptides was more effective than their co-administration (citation omitted), possibly because of enhanced interaction with dendritic cells via the CpG moiety (citation omitted)." (p. 300, col. 1) The state of the art is unclear regarding the use (concentrations, composition (linked or unlinked to antigen), formulations, modes of administration, number of dosages, etc) of these CpG.

The amount of direction or guidance presented in the specification and the

presence or absence of working examples is a hindrance to practicing the claimed invention. Applicants have not provided guidance in the specification toward a method of treating the claimed allergy related disorders, atopic dermatitis or allergic dermatitis comprising the administration first and second compositions that comprise immunostimulatory nucleic acid, of any size or formula, and antigen. As previously stated the specification teaches an increase in immunomodulation in mice (and comprising conversion from a Th2 to a Thl immune response), and treatment of asthma in a mouse model comprising the administration of SEQ ID NO: 10. One skilled in the art would not accept on its face the examples given in the specification as being correlative or representative of the successful treatment of atopic dermatitis or allergic dermatitis or any allergy related disorder in any organism comprising the administration of first and second compositions (CpG of any size and formula and antigen) by any route to a subject during antigen specific immunotherapy in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the biological effects exerted by CpG containing oligonucleotides in any and/or all organisms. The specification as filed fails to provide particular guidance which resolves the known unpredictability in the art associated with effects provided *in vivo* in any and/or all organisms upon administration via any route of any CpG containing oligonucleotides, and further whereby treatment effects are provided in any and/or all organism for atopic dermatitis or allergic dermatitis. The breadth of the claims is very broad and the quantity of experimentation required is undue. The quantity of experimentation required to practice the invention as claimed would require the de novo determination of accessible target sites, modes of delivery and formulations of the CpG to target appropriate cells and/or tissues in any and/or all

organisms, and further whereby treatment effects are provided for the claimed conditions. Since the specification fails to provide particular guidance for the treatment of the claimed atopic dermatitis or allergic dermatitis or allergy related disorders comprising administration of first and second compositions (any CpG and antigen) by any route to a subject during antigen specific immunotherapy is highly unpredictable, it would require undue experimentation to practice the invention over the broad scope as presently claimed.

The examples provided of the induction of various interleukins in spleen, liver or thymus cells are not representative of the successful treatment of any atopic condition (i.e. atopic dermatitis or allergic dermatitis or allergy related disorders) using any CpG oligonucleotide. No correlation is taught in the instant disclosure between the ability of these CpG containing oligonucleotides to induce a Th1 response in vitro (e.g. amount of IL-6 induction) and their ability to treat a representative number of atopic conditions (i.e. atopic dermatitis or allergic dermatitis or allergy related disorders) *in vivo*. An assumed common mechanism of action does not ensure enablement for treatment. Effective delivery to appropriate and concentration of a particular CpG oligonucleotide necessary for providing treatment effects for a particular CpG sequence are still highly unpredictable. The success of treating asthma with SEQ ID NO: 10 is not necessarily representative or correlative of the ability to successfully treat any atopic condition (i.e. atopic dermatitis or allergic dermatitis or allergy related disorders) with the generic recitation of 5'CpG3' sequence. The *in vivo* treatment success for these generic sequences require undue experimentation beyond that provided in the instant disclosure.

It is noted that the specification describes the steps of the claimed method to one skilled in the art, but does not provide any evidence that any of the claimed methods would function *in vivo* or *in vitro*. The issue of correlation is related to the issue of the presence or absence of working examples. Correlation as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a working example, if that example correlates with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute working examples. (see MPEP 2164.02) The pending specification does not set forth such correlations for a working example of the claimed *in vivo* method.

Further, the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art and the level of skill in the art. The state of the art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. The specification must be enabling as of the filing date, not evidence provided several years after the date of filing. The state of the art for a given technology is not static in time. It is entirely possible that a disclosure filed on January 2, 1990, would not have been enabled. However, if the same disclosure had been filed on January 2, 1996, it might have enabled the claims. Therefore, the state of the prior art must be evaluated for each application based on its filing date. (see MPEP 2164.05(a))

5. Claim 19 is not allowed.

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

7. The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record in the parent application, 09/818918, or other related applications.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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